

EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
DISTRICT OF DELAWARE

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NIPPON SHINYAKU CO., LTD.,)	
Plaintiff,)	
)	
v.)	
)	C.A. No. 21-1015 (MN)
SAREPTA THERAPEUTICS, INC.,)	
Defendant.)	
<hr/>)	
SAREPTA THERAPEUTICS, INC. and)	
THE UNIVERSITY OF WESTERN)	
AUSTRALIA, Defendant and Counter-)	
Plaintiff)	
)	
v.)	
)	
NIPPON SHINYAKU CO., LTD. and)	
NS PHARMA, INC., Plaintiff and)	
Counter-Defendants.)	
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EXPERT REPORT OF DR. MICHELLE L. HASTINGS
REGARDING INVALIDITY OF THE UWA PATENTS

September 8, 2023



Michelle L. Hastings, Ph.D.

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I. INTRODUCTION

1. I have been asked by counsel for Nippon Shinyaku Co. Ltd. (“Nippon Shinyaku”) and NS Pharma, Inc. (“NS Pharma,” collectively with Nippon Shinyaku “NS”) to provide an opinion concerning certain claims of U.S. Patent No. 9,994,851 (“the ’851 Patent”), U.S. Patent No. 10,227,590 (“’590 Patent”), and U.S. Patent No. 10,266,827 (“’827 Patent,” collectively with the ’851 Patent and ’590 Patent, the “UWA Patents”). Specifically, I have been asked to analyze the UWA Patents with respect to the written description requirement and provide an opinion as to whether the specification reasonably conveys to a person of ordinary skill in the art (“POSA”) that the inventors had possession of the invention as of the filing date. I have also been asked to analyze the UWA Patents with respect to the enablement requirement and provide an opinion as to whether a POSA would be able to make and use the full scope of the claimed inventions without undue experimentation. Additionally, I have been asked to analyze the UWA Patents with respect to the novelty and non-obviousness requirements and provide an opinion as to whether certain prior art references anticipate and/or render obvious one or more claims of the UWA Patents. This Opening Expert Report (“Report”) presents the opinions I have formed at this time. If asked, I will testify based upon my study of the materials identified in Exhibit 1 and throughout this Report, as well as my personal knowledge and experience on this subject matter.

2. I understand from counsel for NS (“counsel”) that I may be provided additional information as this case proceeds, including rebuttal opinions that may be offered by experts for Sarepta Therapeutics, Inc. (“Sarepta”) and the University of Western Australia (“UWA”). Accordingly, I may need to change or augment my analysis and opinions in light of any new information or evidence that is presented after this Report. I expressly reserve the right to do so, including to opine on any evidence raised in those rebuttal opinions.

TABLE 39

SEQ ID name	Antisense oligonucleotide	Sequence	Ability to induce skipping
191	H53A (+45+69)	CAU UCA ACU GUU GCC UCC GGU UCU G	Faint skipping at 50 nM
192	H53A (+39+62)	CUG UUG CCU CCG GUU CUG AAG GUG	Faint skipping at 50 nM
193	H53A (+39+69)	CAU UCA ACU GUU GCC UCC GGU UCU GAA GGU G	Strong skipping to 50 nM
194	H53D (+14-07)	UAC UAA CCU UGG UUU CUG UGA	Very faint skipping to 50 nM
195	H53A (+23+47)	CUG AAG GUG UUC UUG UAC UUC AUC C	Very faint skipping to 50 nM
196	H53A (+150+176)	UGU AUA GGG ACC CUC CUU CCA UGA CUC	Very faint skipping to 50 nM
197	H53D (+20-05)	CUA ACC UUG GUU UCU GUG AUU UUC U	Not made yet
198	H53D (+09-18)	GGU AUC UUU GAU ACU AAC CUU GGU UUC	Faint at 600 nM
199	H53A (-12+10)	AUU CUU UCA ACU AGA AUA AAA G	No skipping
200	H53A (-07+18)	GAU UCU GAA UUG UUU CAA CUA GAA U	No skipping
201	H53A (+07+26)	AUC CCA CUG AUU CUG AAU UC	No skipping
202	H53A (+124+145)	UUG GCU CUG GCC UGU CCU AAG A	No skipping

“Very faint skipping at 50 nM” does not meet the UWA Patent’s definition of “efficient antisense molecule.” *See* ’851 Patent at 33:13-16 (“Our definition of an efficient antisense molecule is one that induces strong and sustained exon skipping at transfection concentrations in the order of 300 nM or less.”). In my opinion, the sole disclosure of SEQ ID NO: 195 is insufficient to support the broad genus of up to 10¹⁴ possible antisense oligonucleotides encompassed by the claims of the UWA Patent.

51. Moreover, as explained by Dr. Wood, exon-skipping activity can vary greatly even among antisense oligonucleotides sharing a common nucleotide sequence. Wood Report ¶¶ 75-86; *see also* Wood Interference Declaration ¶¶ 68-77. Therefore, a POSA would not consider that the

[REDACTED]

named inventors were in possession of a genus of antisense oligonucleotides having exon skipping activity merely because they shared 12 consecutive bases of SEQ ID NO: 195.

52. Indeed, there is no indication in the UWA Patents that comprising 12 consecutive bases of SEQ ID NO: 195 is even important to exon 53 skipping. The sole disclosure of “12 bases” in the specification of the UWA Patents is in a passage discussing exon 19 skipping. ’851 Patent at 23:58-24:3 (“With some targets such as exon 19, antisense oligonucleotides as short as 12 bases were able to induce exon skipping, albeit not as efficiently as longer (20-31 bases) oligonucleotides.”) The UWA Patents make no mention of “12 bases” with respect to exon 53 skipping or SEQ ID NO: 195.

53. Further, the phrase “12 bases” is used in the above cited passage to describe overall antisense oligonucleotide length. It does not use the term “12 bases” to describe a “base sequence” component included within a longer antisense oligonucleotide with additional bases, as set forth in the UWA Patent claims. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

54. Furthermore, as explained by Dr. Wood, the deletion of as few as two nucleotides from an antisense oligonucleotide that induces exon skipping or changes to a significant number of nucleotides in an antisense oligonucleotide that induces exon skipping can reduce or eliminate such activity altogether. Wood Report ¶ 81; *see also* Wood Interference Declaration ¶ 74; Wilton, Steve D., and Susan Fletcher. “Antisense oligonucleotides in the treatment of Duchenne muscular dystrophy: where are we now?” *Neuromuscular Disorders* 15.6 (2005): 399-402 (“Displacing the annealing site of an AO by only a few bases can alter its exon skipping potential by more than an

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REPLY EXPERT REPORT OF DR. MICHELLE L. HASTINGS
REGARDING THE INVALIDITY OF THE UWA PATENTS

October 27, 2023



Michelle L. Hastings, Ph.D.

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used in the method. Preferably, the length of the antisense molecule is between 17 to 30 nucleotides in length.

'851 Patent at 25:65-26:3.⁴ Per the express teaching of the UWA Patents, an AO may be as short as 10 bases long. It follows that a “weasel” AO designed to target two different regions of human exon 53 can be as short as 20 bases, thus falling within the scope of “20 to 31 bases” recited in the UWA Patent claims.⁵

B. Dr. Dowdy’s Alternative “Universe of Candidate PMOs” Is Still Extremely Large

18. According to Dr. Dowdy, the “structural requirements” of the claims of the UWA Patents “collectively identify a limited group of candidate PMOs, each of which a POSA would have been able to visualize from the disclosures of the Wilton Patents.” Dowdy Rebuttal ¶ 57. To arrive at this purported “limited group,” Dr. Dowdy assumes that the entirety of the AO must “have 100% or near 100% complementarity” to the “target region of exon 53 of the human dystrophin pre-mRNA.” *Id.* ¶ 41.⁶ For those with “near 100% complementarity,” Dr. Dowdy allows for one mismatch or insertion. *Id.* ¶ 57.⁷ With these assumptions, Dr. Dowdy arrives at “**22,586 PMOs**

⁴ The statement that “any length of nucleotides within this range may be used” cannot provide written description support for the claimed “20 to 31 bases” limitation as I am informed that description that merely renders an invention obvious does not satisfy the written description requirement.

⁵ I discuss the specific weasel AOs that I designed for the CERI experiments further below.

⁶ As noted above, I disagree with this interpretation because it is contrary to the Court’s construction. I also disagree with Dr. Dowdy’s interpretation that for the ’851 patent, the entirety of the antisense oligonucleotide must be “within” +23+69. As properly construed, only the “base sequence” needs to be “within” the target region, and again, the “base sequence” *need not* span the entirety of the antisense oligonucleotide.

⁷ Dr. Dowdy did not allow for any such “mismatch or insertion” in his estimation of ’212 Popplewell’s “limited group” of PMOs that a POSA would purportedly “at once envisage” (Dowdy Opening ¶¶ 311-14)—despite ’212 Popplewell’s *express* teaching that the “base sequence can vary from the above sequence at up to two base positions.” Hastings Rebuttal ¶ 43.

potentially within the scope of the claims of the '851 Patent and **44,406 PMOs** potentially within the scope of the '590 and '827 Patents.” *Id.* ¶ 58. This is still a vast number of possible PMOs. In my opinion, a POSA reading the specification of the UWA Patents would not have recognized that the inventors possessed all of the PMOs in this vast genus.

19. As noted, to arrive at this purported limited genus (which it is not), Dr. Dowdy allows for **only one** mismatch or insertion. *Id.* ¶ 57. According to Dr. Dowdy, “such a mutation could have been employed to account for a SNP that may exist in the intended target region.” *Id.*



